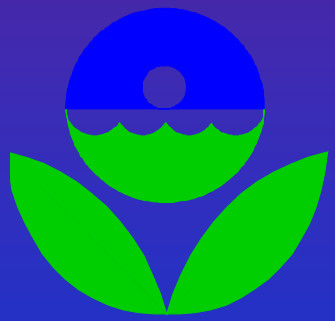
Nitrate Health Effects



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Two Goals

- Describe USEPA's judgement of risks from nitrate (and nitrite) in drinking water
- Discuss USEPA's review of the current nitrate (and nitrite) MCL

USEPA's View of Nitrate (and Nitrite) Toxicity, Briefly

- Nitrate and nitrite effects are related
- Oral ingestion can lead to methemoglobinemia in infants
  - First described in 1945
  - Reference Dose established 1991
  - Basis of nitrate and nitrite MCLs
- Not a human carcinogen (2002)

Toxicity Concerns from Nitrate in Drinking Water

- Methemoglobinemia
- Cancers
- Developmental effects
- Hypothyroidism

What is Methemoglobinemia?

- Aka “Blue Baby Syndrome”
- Inhibition of blood’s ability to carry oxygen
  - Lips and skin can turn bluish (cyanosis)
- Can be caused by several agents
- Normal hemoglobin is converted to methemoglobin, which cannot carry oxygen
  - 10-20% methemoglobin yields bluish skin
  - 25-40% yields hypotension, rapid pulse and breathing
  - > 50% can be fatal

Methemoglobinemia Causes

- Can be congenital
- Use of aromatic amine drugs, like Dapsone and benzocaine
- Ingestion of nitrites or chlorates

Nitrate, Nitrite and Methemoglobinemia

- Nitrate does not cause methemoglobinemia by itself
- Nitrate must be converted to nitrite by bacteria in the gut
- Nitrite enters bloodstream, reacts with hemoglobin to make methemoglobin

Infants and Methemoglobinemia

- Infants (< 4-6 months) are most sensitive
  - Low stomach acidity allows better bacterial growth
  - Infant hemoglobin more easily converted
  - System to return methemoglobin to hemoglobin immature
- Methemoglobinemia in infants typically associated with diarrhea
  - Suggests a fecal association

Children, Adults and Methemoglobinemia

- Rare, typically from accidental nitrate or nitrite ingestion at high (>1000 mg) levels
- Some families are congenitally predisposed
  - Lack methemoglobin reductase or other enzymes
- Otherwise, not a public health issue at ambient levels

Methemoglobinemia Epidemiology

- Methemoglobinemia in infants most studied
- Data sets showing increasing levels of methemoglobinemia with nitrate were from wells with bacterial contamination
- Clinical studies of nitrate exposure alone showed little or no methemoglobinemia
- Bacterial contamination or illness considered a cofactor

Methemoglobinemia in California

- Agency for Toxic Substances and Disease Registry did an assessment at the request of CA DHS (now DPH) in 2000
- 42 total methemoglobinemia cases over 13 years studied
  - None specifically associated with nitrate
  - Four were located in areas where wells are used
- National figures similar- rare to find a clear, unique association with drinking water nitrate

Is Nitrate a Human Carcinogen?

- USEPA does not currently believe so, based on lack of supporting data and substantial negative data
- Theory is that nitrate --> nitrite --> nitrosamines
  - Nitrosamines known to cause cancer
  - But nitrate/ nitrite not demonstrably so
  - Also, nitrosamines produced endogenously
- Animal toxicity studies show nitrosamines cause cancer, but not nitrate or nitrite alone
- Human epidemiology studies are equivocal or conflicting
- Bottom line: no smoking gun

An Example: Iowa Women's Health Study

- Long-term epidemiological study of >21,000 women
  - Some water quality data from 1955-1988
  - Tracked health problems from 1989-1998
- Found some positive correlations between certain cancers and DW nitrate
- Found some negative correlations, too
- Statistically weak
- Net effect = zero

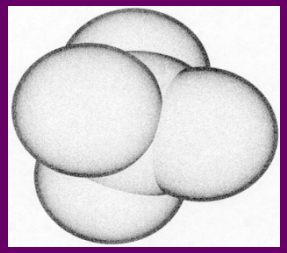
Developmental Damage from Nitrate?

- A number of epidemiological studies have examined different types of developmental damage versus nitrate exposure
  - Miscarriage, stillbirth
  - Anencephaly, neural tube defects
- Human data tend to be negative
  - Some weakly positive results
- High nitrate doses in animals do show effects

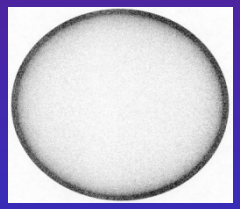
Hypothyroidism?

- Nitrate is a goitrogen, affects thyroid function
  - Similar effects as perchlorate
  - Sensitive groups are pregnant women, infants
- Iodide mimic
  - Inhibits iodide uptake by thyroid
- Not as potent as perchlorate (1/240)
- But occurrence is substantially higher (>1000 x)
- Perhaps ~ 5-fold more risky than perchlorate?
  - http://www.epa.gov/oig/reports/2010/20100419-10-P-0101.pdf
- Not much studied

Nitrate Mode of Action



Nitrate



Iodide

Pituitary

TSH

THYROID GLAND

T4 and T3

The Safe Drinking Water Act Directs EPA's DW Regulations

- Maximum Contaminant Level Goal
  - **Not enforceable, but directs MCL selection**
  - **"Each MCLG...shall be set at the level at which no known or anticipated adverse effects on the health of persons occur and which allow an adequate margin of safety"**
- National Primary Drinking Water Regulations
  - **Enforceable**
  - **Set as close as feasible to MCLGs**
  - **Feasible analytical methods and treatment technologies**
  - **Administrator can adjust MCL for cost reasons**
- Other regulatory applications generally not considered

Regulatory Construction

- A drinking water regulation needs several things:
- Health risk information
  - Is it a problem at the levels found?
- Suitable quantitative analytical methods
- Occurrence information
  - What levels is it found at?
  - Where, when?
- Feasible treatment technologies
- Holistic cost information (i.e., for everything)
- Benefit-cost analysis (is it worth it?)

Regulatory Risk Assessment for Nitrate

- Most data for infant methemoglobinemia
  - Acute (*vs.* chronic) health endpoint
- Infants are the most sensitive subpopulation
  - Children and adults very rarely affected
- Data support a threshold model
  - EPA set a Reference Dose (RfD), below which no adverse effects expected
  - RfD = NOAEL = 10 mg nitrate-N/ day

USEPA's Nitrate MCL is 10 mg/L

- For drinking water, the Maximum Contaminant Level of 10 mg/L nitrate-N is considered safe over a lifetime exposure
  - 10 mg/L nitrate-N is equivalent to 45 mg/L nitrate (CA DPH MCL)
- Maximum Contaminant Level Goal is also 10 mg/L
  - Based on prevention of methemoglobinemia in infants
  - Set at Reference Dose

Nitrite MCLG and MCL at 1 mg/L

- 1 mg/L nitrite-N
  - CA DHS MCL 1 mg/L for total nitrite
- Based on estimated average infant nitrate metabolism to nitrite
- Health effects and risk assessment same as for nitrate

- Note: If nitrate/nitrate were carcinogenic, then only weakly so. MCLs should be protective

Will USEPA Change Its MCLs?

- EPA reviews the nitrate and nitrite MCLs as part of it “6-year review of DW regulations”
- Most recent 6-year review found no new health information to indicate a need to revise MCLs
- Unlikely to reconsider carcinogenicity unless new data become available

PWS Nitrate Compliance in CA

- 37 community water systems in CA serving about 12,000 people are currently out of compliance with the nitrate MCL
- 73 non-community systems (stores, packers, schools, etc) have current MCL violations, too
- There are no current nitrite MCL violations in CA
- Of those systems with violations, most are on consent orders with plans and timelines for return to compliance

Tangential Effects of Nitrogen in Water Sources

- “Reactive” nitrogen in drinking water surface sources may be indirectly problematical
- Nitrogen as an essential plant nutrient can support excessive algal growth
- Some algae (blue green algae) are toxic or produce toxins
- Algae in general clog filters and cause diurnal pH changes that adversely affect water treatment

Reactive Nitrogen as a Disinfection Byproduct Precursor

- Nitrogenous materials, including nitrate, can be oxidized to N-nitroso dimethyl amine (NDMA)
- NDMA is a known carcinogen
  - 10^{-6} risk @ 0.7 ng/L
- Formed from chlorination or chloramination of wastewaters and source waters with Nr
- Monitoring shows 25% of water systems affected

Treated *Wastewater* DBPs

- N-organics + chlorine => nitrogenous DBPs
  - Nitrosamines (e.g., NDMA)
  - Haloacetonitriles
  - Halonitromethanes
  - Organic chloramines
  - Chloropicrin
  - Halofuranones (MX analogs)
- Many of these are known carcinogens
- Can be issues for drinking water intakes below wastewater outfalls

Possible Nitrate Health Studies

- Could look at nitrate's relationship to thyroid function in newborns
  - Data collected at birth
  - Have to control for inadequate dietary iodide
- Might be useful to assess well water quality for both nitrate and pathogenic bacteria, especially for private wells
  - Most risky if both found